the formula RHgCl; this may be due to contamination with derivatives of the type R_2Hg.

1-Glycosylbenzimidazoles.—A suspension of the finely powdered chloromercuri compound in xylene (80 ml./g.) was dried by slow distillation of one-third of the xylene, and to the residual suspension was added a slight excess of triacetyl-D-ribofuranosyl chloride[8] or tetraacetylglucosyl bromide. The mixture was refluxed gently for 1.5–2 hours, then cooled and diluted with two volumes of petroleum ether (b.p. 30–60°). The precipitate was washed with petroleum ether, dried and extracted with cold chloroform. The extract was washed with 30% potassium iodide and with water, dried over sodium sulfate, and evaporated under reduced pressure to a sirup, which was dissolved in methanol and treated with an excess of methanolic ammonia (saturated at 0°). The solution was kept overnight in the refrigerator, then evaporated to dryness and the residual glycosylbenzimidazole crystallized from water or dilute aqueous ethanol. If difficulty was experienced in crystallizing the compound it was isolated as the picrate and regenerated by the use of an anion-exchange resin.[6]

1-β-D-Ribofuranosyl-5,6-dimethylbenzimidazole Picrate.—Prepared in aqueous ethanolic solution, the picrate formed yellow needles, m.p. 172–174°, which did not depress the melting point of an authentic sample, m.p. 169–171° at the same rate of heating. At this rate of heating a sample of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole picrate had m.p. 207–210°.

Anal. Calcd. for $C_{20}H_{21}O_{11}N_5$: N, 13.8. Found: N, 14.1.

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(8) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

N-Acylamino Acids, A New Class of Resolving Agents[1]

BY H. D. DEWITT AND A. W. INGERSOLL

Various optically active N-acylamino acids were tested as agents for the resolution of racemic bases. N-Acetyl-L-leucine resolved α-phenylethylamine and α-*p*-tolylethylamine. N-Acetyl-3,5-dibromo-L-tyrosine resolved α-phenylethylamine and α-phenyl-*n*-propylamine. Certain other amines were not resolved by these agents. N-Acetyl-3,5-dibromo-DL-tyrosine was resolved by α-phenylethylamines.

The number and structural variety of available acidic resolving agents is quite small. (+)-Tartaric acid, (+)-camphor-10-sulfonic acid and (+)-α-bromocamphor-π-sulfonic acid are extensively used, while fewer than a dozen others have been used a few times. Most of these acids are available mainly in one active form; it is desirable to have both active forms.[2] Also, most of the acids are not physically well suited for convenient preparation and recovery.

It seems feasible to attempt to extend the list of resolving agents considerably by inclusion of suitably chosen N-acylamino acids. Many of these exhibit desirable general properties, particularly chemical stability, moderate acid strength, crystallizing power, and ease of preparation and recovery. Various combinations of parent amino acids with common acyl and sulfonyl groups should provide a desirable range of molecular weights and solubilities. At the outset it has seemed most practical to investigate derivatives of readily available natural acids, such as L-leucine, L-tyrosine and L-glutamic acid, but facile resolutions of the acetyl derivatives of 3,5-dibromo-DL-tyrosine, DL-tyrosine, DL-phenylalanine[3] and other common synthetic amino acids indicate that both active forms can be made available if desired.

Resolutions of *dl*-α-fenchylamine by use of the active acetyl derivatives of leucine,[4] valine[3] and phenylalanine[3] have already been reported. In continuation, acetyl-L-leucine was tested with seven other amines, namely, α-phenylethylamine, α-*p*-tolylethylamine, α-phenyl-*n*-propylamine, α-*p*-chlorophenylethylamine, α-*p*-xenylethylamine, phenylisopropylcarbinamine and β-octylamine. Satisfactory resolutions were obtained with the first two of these; the others formed highly crystalline salts but were not resolved in common solvents. The resolution of α-phenylethylamine is particularly useful, the (+)-form being obtained in 80% yield.

The acetyl and *p*-nitrobenzoyl derivatives of L-glutamic acid did not effect resolutions of any of the amines tested. The salts in general were too soluble or difficult to crystallize, although Howe and Sletzinger[5] recently have used the *p*-nitrobenzoyl derivative for the resolution of isoamidone, the first reported use of this class of agents.

N-Acetyl-L-tyrosine is easily made but is too soluble for convenient purification and recovery. This disadvantage was overcome by dinitration or dibromination of L-tyrosine and subsequent N-acetylation. N-Acetyl-3,5-dinitro-L-tyrosine salts are highly colored and otherwise unsuitable. N-Acetyl-3,5-dibromo-L-tyrosine, however, effected ready resolutions of α-phenyl-*n*-propylamine and α-phenylethylamine. The remaining amines tested formed well crystallized salts but were not resolved. The resolution of α-phenylethylamine gave the (−)-form in 78% yield and is thus complementary to that with acetyl-L-leucine. N-Acetyl-3,5-dibromo-DL-tyrosine, prepared from racemized L-tyrosine, was readily resolved by (−)- and (+)-α-phenylethylamines, thus making both forms available.

The proportion of successful resolutions effected thus far with N-acylamino acids (five of ten tried) is not exceptional but the successful examples fortunately afford convenient procedures for several individually important amines. The work is being continued.

(1) Taken from the Ph.D. thesis of H. D. DeWitt, September, 1950.

(2) M. S. Raasch and W. R. Brode, THIS JOURNAL, **64**, 1112 (1942); A. W. Ingersoll and J. R. Little, *ibid.*, **56**, 2123 (1934); related work is reviewed.

(3) L. R. Overby and A. W. Ingersoll, *ibid.*, **73**, 3363 (1951).

(4) A. W. Ingersoll and H. D. DeWitt, *ibid.*, **73**, 3360 (1951).

(5) E. E. Howe and M. Sletzinger, *ibid.*, **71**, 2935 (1949).

Experimental

Preparation of N-Acetyl-3,5-dibromo-L-tyrosine.—Technical grade L-tyrosine (*ca.* 96%) was brominated in 1-mole lots in 5 parts of glacial acetic acid with slightly more than 2 moles of bromine by the method of Zeynek.[6] On this scale it was desirable to add the bromine gradually with stirring and complete the reaction by warming to 80–90°. After slow cooling the sparingly soluble hydrobromide was then easily filtered and washed free of color with cold acetic acid. The filtrate, which contains part of the product, was suitably used as solvent for brominating a second and third lot. The hydrobromide was dissolved in water and the amino acid precipitated with the calculated amount of ammonia; yield 75–83%. Without further purification the material was acetylated as usual and obtained initially as tan microcrystals; over-all yield 65–68%. It is easily soluble in organic solvents and was best purified by crystallization (carbon) from water or preferably 15% methanol as colorless glistening plates (hemihydrate), m.p. 118–120° (dec.); $[\alpha]^{25}D$ +34.5° (*c* 4, methanol); solubility in water, 0.25 per 100 cc. of solution at 25°. It titrates as a diacid (glass electrode) with inflection points at *p*H *ca.* 5.6 and 9.3.

Anal. Calcd. for $(C_{11}H_{11}O_4NBr_2)_2 \cdot H_2O$: neut. equiv. (diacid), 194.9; N, 3.59. Found; neut. equiv., 195.0; N, 3.55.

N-Acetyl-3,5-dibromo-DL-tyrosine was prepared similarly from DL-tyrosine.[7] It is much less soluble than the L-form and was crystallized from methanol; m.p. 213–215° (dec.).

Anal. Calcd. for $C_{11}H_{11}O_4NBr_2$: neut. equiv. (diacid), 190.5; N, 3.68. Found: neut. equiv., 190.9; N, 3.62.

Resolution of α-Phenylethylamine with Acetyl-L-leucine.—The reagents (1 mole) were combined in 250 cc. of water and the salt dissolved in 850 cc. more hot water. Successive crops were systematically recrystallized from (initially) 6–7 parts of water and after two series gave 130.5 g. (89%) of the (+)-amine salt as narrow prisms, m.p. 185–190° (dec.); $[\alpha]^{25}D$ −8.8° (*c* 4, methanol); solubility in water at 25°, 5.57 g./100 cc. The foot fractions gave fine needles of the considerably more soluble (−)-amine salt but this was not completely purified. The (+)-amine salt was decomposed as usual and the amine was extracted with benzene, dried and distilled; yield 80%, based on *dl*-form. The amine had $[\alpha]^{25}D$ +39.2° (without solvent, d^{25}_4 0.94) in agreement with reported values.[8] The impure (−)-amine obtained similarly from the more soluble salt had $[\alpha]^{25}D$ −33.6°. Acetylleucine satisfactory for re-use was recovered in 94% yield.

Resolution of α-*p*-Tolylethylamine with Acetyl-L-leucine.—The reagents (0.5 mole) were combined in 500 cc. of water and the salts fractionated as usual. The isomeric salts were not greatly different in appearance and solubility but after four crystallizations the (+)-amine salt was obtained (63%) as narrow prisms, $[\alpha]^{25}D$ −12.7° (*c* 4, water). The (−)-amine salt formed fine needles but was not purified. The (+)-amine was obtained as usual and had $[\alpha]^{25}D$ −34.0° (without solvent, d^{25}_4 0.917).[9] The resolution is rather less convenient than that with (+)-camphoric acid.[9]

Resolution of α-Phenylethylamine with Acetyldibromo-L-tyrosine.—The reagents (0.1 mole) were combined in 150 cc. of water (carbon) and the initial crop (27 g.) was recrystallized twice from 10 parts of water. The less soluble (−)-amine salt (17.8 g.) forms small flat prisms, $[\alpha]^{25}D$ +43.8° (*c* 4, methanol), unchanged after recrystallization. Additional amounts (total 20.6 g., 87.5%) were obtained from intermediate fractions. The amine from this salt was recovered as usual and had $[\alpha]^{25}D$ −39.2°.[8] Evaporation of the mother liquors gave fine needles of (+)-amine salt of which one fraction had $[\alpha]^{25}D$ +48.0° (*c* 4, methanol) but no attempt was made to purify this salt. Acetyldibromo-L-tyrosine was readily recovered.

Resolution of α-Phenyl-*n*-propylamine with Acetyldibromo-L-tyrosine.—The reagents (0.1 mole) were combined in 900 cc. of water and the resolution conducted substantially as in the preceding example. The less soluble (−)-amine salt forms fine needles, $[\alpha]^{25}D$ +52.2 ± 0.3°; yield 83%. The remaining salt was much more soluble and was not purified. The (−)-amine from the less soluble salt had b.p. 202–206° (752 mm.), $[\alpha]^{25}D$ −12.2° (*c* 4, ethanol). No previous resolution of this amine has been found.

Resolution of Acetyldibromo-DL-tyrosine.—The acid and (−)-α-phenylethylamine (0.05 mole) were combined in 100 cc. of water and the less soluble salt was twice recrystallized (carbon) as previously described. For decomposition the pure salt (9.2 g.) in 150 cc. of boiling water was treated with a slight excess of concentrated hydrochloric acid. Pure acetyldibromo-L-tyrosine hemihydrate (5.5 g., 58% of the DL-form taken) crystallized on cooling. It had m.p. 119–120° and $[\alpha]^{25}D$ +34.7° (*c* 4, methanol) in close agreement with the product from natural L-tyrosine. The crude D-form (9.5 g.), $[\alpha]^{25}D$ −22.5°, was similarly recovered from the resolution liquors and converted to the (+)-amine salt. The twice recrystallized salt (7.5 g.) on decomposition gave pure acetyldibromo-D-tyrosine hemihydrate (5.0 g., 52%) with m.p. 119–120° and $[\alpha]^{25}D$ −34.3°, in close agreement with values for the antipode. These resolutions are satisfactory but do not proceed quite as readily as the reciprocal resolution of the amine.

(6) R. Zeynek, *Z. physiol. Chem.*, **114**, 275 (1921); C. T. Mörner, *ibid.*, **88**, 124 (1913).

(7) M. Fling, Thesis, Iowa State College, 1946; *C. A.*, **44**, 4050 (1950).

(8) A. W. Ingersoll, *Org. Syntheses*, **17**, 80 (1937).

(9) A. W. Ingersoll and F. B. Burns, THIS JOURNAL, **54**, 4712 (1932).

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[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

The Resolution of Amino Acids. IV. Lysine[1]

BY F. J. KEARLEY AND A. W. INGERSOLL

DL-Lysine has been resolved into both forms by means of dibenzoyltartaric acid, with recovery of the active forms as hydrochlorides in about 65% yields. Resolution by means of the new agent, N-acetyl-3,5-dibromo-L-tyrosine, even more easily gave L-lysine monohydrochloride in good yield. Attempted resolutions of lysine with numerous other active acids and of diacetyllysine with various active bases were unsuccessful.

The first resolution of lysine was effected by Berg,[2] the L- and D-forms being obtained alternately through the normal (+)- and (−)-camphorates. More recently the asymmetric anilide synthesis induced by papain has been successfully applied to the carbobenzoxy derivative of lysine by Borsook, *et al.*,[3] and to the isobutyryl and *n*-caproyl derivatives by Doherty and Popenoe.[4] Also, by using a repurified preparation of hog kidney enzyme, Greenstein and associates[5] have adapted their general method of selective hydrolysis to the resolution of lysine through the chloroacetyl derivatives.

The method of Berg, with minor modifications,[6,7]

(1) Taken from the Ph.D. thesis of Francis J. Kearley, September, 1950.

(2) C. P. Berg, *J. Biol. Chem.*, **115**, 9 (1936).

(3) H. Borsook, C. L. Deasy, A. J. Haagen-Smit, G. Keighley and P. H. Lowy, *ibid.*, **176**, 1383 (1948); **184**, 529 (1950).

(4) D. G. Doherty and E. A. Popenoe, *ibid.*, **189**, 447 (1951).

(5) J. P. Greenstein, J. B. Gilbert and P. J. Fodor, *ibid.*, **182**, 451 (1950).

(6) N. Weissman and R. Schoenheimer, *ibid.*, **140**, 779 (1941).

(7) A. Neuberger and F. Sanger, *Biochem. J.*, **38**, 125 (1944).